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14. ABSTRACT The training grant goals are to provide a broad range of opportunities for undergraduate students to participate in general clinical and basic science breast cancer research under the mentorship of experienced physician scientists in an academic institution. In the third year of the training grant, from May to August of 2005, 5 undergraduate students participated in original clinical or basic science research projects in the Department of Radiation Oncology. The students met or exceeded their expected goals of learning the principles of research, completing data collection and proceeding to analysis of the results. All students presented their research results at a minsymposium for the departmental staff and faculty. The quality of applicants was high and their performance on their research projects was excellent. Three projects have been submitted to national research meetings. Other projects are in press or manuscripts are in preparation.					
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Annual Summary Report
April 15, 2005 – April 15, 2006

DAMD17-03-1-0309

Undergraduate Summer Training Program in Investigating the Role of Radiation Therapy
Breast Cancer Clinical and Translational Research

Principal investigator: Eleanor E. R. Harris, MD

I. Introduction:

This is the third and final annual summary report for the above named training grant, focusing on the third year of research activities and summarizing the accomplishments of the grant period from 2003 to 2006. The training grant goals are to provide a broad range of opportunities for undergraduate students to participate in general clinical and basic science breast cancer research under the mentorship of experienced physician scientists in an academic institution. The students were exposed to the research process from design to analysis to authorship, with the goal of instilling both an understanding of the research process and of fostering a lasting commitment to the pursuit of breast cancer research. In the summer of 2005, five undergraduate students from the University of Pennsylvania conducted an original research clinical or laboratory project under the supervision of a mentor. Some projects are ongoing and others are being presented at scientific meetings and submitted for peer-reviewed publication. In their evaluations, the students expressed a high degree of satisfaction with their experience. As principal investigator, I was highly impressed with the quality of work and dedication these students exhibited. All five students exceeded expectations for the program's goals.

II. Body:

The goal of the training grant is to recruit undergraduate students for the summer research session, and to provide each the opportunity to participate in a research project from start to finish. The initial phase is recruitment, which began in January 2005. Through contacts at the University of Pennsylvania School of Arts and Sciences, I was able to recruit an excellent pool of applicants from which to choose the five trainees. Recruitment flyers (attached) were submitted to the chairman of the Biological Sciences department, to the undergraduate premedical advisors office and to the Center for Undergraduate Research and Fellowships, the office which coordinates all research opportunities for the school. I received 56 inquiries and 29 complete applications for the five positions, which was the highest interest level of all three years of the grant. The caliber of applicants reflected academic excellence and diversity. Among the applicants, 21 were women and 8 were men. Eleven of the applicants would be entering their senior year, 14 were entering junior year, and 4 were upcoming sophomores. Prior laboratory experience and science course were required for any applicants wishing to conduct basic science research, but no specific background was required for students wishing to pursue clinical research. I selected six applicants from the pool and three alternates, and five students were accepted into the program. These included were three women and two men, three upcoming seniors, and two upcoming juniors. Three students were assigned clinical research projects, and two were assigned laboratory projects.

Once the applicants were selected, they reviewed a project list giving the titles of possible research projects (attached). Prior to the beginning of the summer session, they were asked to review the list and select any projects titles they were interested in working on. I met with each candidate individually to discuss in greater detail the study questions and design involved in any of the projects they had found interesting. Students then submitted three choices for projects, and I assigned each one a specific topic. The students were then shown how to perform a Medline search and given copies of reference chapters from textbooks to read. Each was asked to independently research their specific topic by finding relevant background studies in the medical literature. I reviewed with them their background searches and provided them with any additional references they needed in order to learn about their topic. Once the students began their research in May 2005, they knew what their specific topic would be and had reviewed the relevant medical literature. During the summer session, all students were expected to spend at least one day shadowing a physician in the clinic to provide them with some experience of the clinical nature of breast cancer patients' experiences.

The summer session was opened with an orientation session (agenda attached). This included an orientation to the hospital and Radiation Oncology Department, regarding payroll procedures, hospital and departmental policies, HIPAA and IRB training, departmental and hospital database access and utilization procedures, and the students were taken for hospital identification badges. The orientation included a series of lectures given by members of the Cancer Center faculty on breast cancer, radiation therapy and systemic therapy for breast cancer, clinical and laboratory research practices and documentation, clinical trials, and biostatistics. The trainees also heard presentations from residents and medical students who had done research work in the department as an example of the types of projects they would themselves be working on. The students then began their individual projects under the direction of their individual mentors. Three mentors participated in the program: Eleanor Harris MD, Lawrence Solin MD, and Gary Kao MD PhD; each mentor was assigned one or two students.

For clinical research projects, the first stage of work was to develop a study hypothesis and study design under the guidance of the faculty mentor. This step was completed in the first week of the project. For each clinical project, the students were provided with the pertinent patient list and an Excel spreadsheet containing numerous data points derived from the department's extensive breast cancer database. These data files were saved to a password protected departmental server and each student was assigned a unique username and password through which to access their specific data files and on which to save their work. Students were assigned desk with a computer workstation at which to work. Students then developed a list of data points they needed for their study and edited their spreadsheets. Students were also given the opportunity, with guidance, to write and submit standard requests for Institutional Review Board approvals, which in all cases involved a simple expedited review process.

The second stage of work was data collection. Each student searched through the relevant medical records for the needed data and entered that data on their spreadsheets on an ongoing basis. During this phase, the students needed to think about their hypothesis and ensure that the data being obtained was adequate to analyze the study question. Each student kept a diary of their daily activities and met once a week with their mentor to discuss their progress

and ask any questions that had arisen. I met with all three students weekly as well in order to assess the progress of each project. Either the faculty mentor or I met once weekly with the two students in the lab, to review their weekly logs and assess their progress. These students were under daily supervision of their faculty mentor, as they worked side by side with him in the lab.

The third stage of work was data analysis. For this, most of the students worked with a statistician. The students discussed with the statistician how to organize their data files for statistical analysis, then submitted their data files to the statistician for computation. Simple analyses like descriptive statistics were sometimes performed by the student. Each student began work on an abstract in standard format (Introduction; Methods; Results; Conclusions).

The final stage of work was abstract production and presentation of their work. A research symposium was organized and held within the department at which each student gave a 20 minute Powerpoint presentation of their research project (attached). Each gave an introduction, followed by methods, results and conclusions.

At the end of the summer session, each student turned in their diaries and were asked to complete an evaluation form (attached) of the program. Their comments were generally positive, rating the quality of the introduction and orientation, mentoring and oversight, scope and interest level of the projects, experiences shadowing a clinician, interaction with other students and residents and facilities all in the excellent or good category. A problem in timely chart acquisition from previous years was solved by relocating all of the study charts to a central location in the department. Many students felt that the research experience had solidified their interest in a medical or research career.

All but one of the student's projects will be presented or published most likely in 2006. One student has continued on in the laboratory she worked in during the summer. Three of the students projects have been submitted for presentation at the annual meeting of the American Society for Therapeutic Radiology and Oncology (ASTRO). Four projects are currently being written up as manuscripts for peer-reviewed publication with submission anticipated within the year.

III. Key Research Accomplishments:

Undergraduate researchers, 2005:

1. Sundeep Kasi: The Impact of Anemia on Local Control and Survival of Breast Cancer Patients Undergoing Breast Conservation Therapy.

Mentor: Eleanor Harris, MD

Summary: This project involved reviewing nearly 1500 charts in order to record the hemoglobin levels before, during and after radiation for breast conservation treatment. Sundeep worked diligently and efficiently and completed this massive data collection effort ahead of schedule. He organized the data and submitted it to the statistician for analysis. This phase is also complete and the project has been submitted for presentation at the 2006 ASTRO meeting. Although Sundeep is back in class for the fall semester, he assisted with the abstract preparation. The manuscript is also in progress and will be submitted for peer-review publication in the next few months. Sundeep has applied this summer for several new research opportunities and will be taking his MCAT in preparation for applying to medical schools.

2. Daniel Feldman: Analysis of Metastatic Disease by Histological Subtype in Early-stage Breast Cancer Patients

Mentor: Eleanor Harris, MD

Summary: This project also involved reviewing about 1500 charts to determine outcome status on women treated with breast conservation therapy with invasive ductal carcinoma, which was used as the control group for women with other unusual histologies, including tubular, medullary, colloid and others. Dan used the medical charts as well as the hospital electronic databases to record the presence of Metastatic disease, the patterns and locations of metastases and the outcomes after recurrence. Dan completed his data collection and organized the data for the statistician. Data analysis has been completed and the manuscript is in preparation for peer-review publication. Dan was so enthusiastic about his summer project that he asked to work during the semester on a new project. Dan collected data on the cosmesis and complications of women with DCIS who had breast conservation therapy. This project will be completed by one of our residents and we anticipate that the manuscript will be completed this year. Dan has applied for both research and clinical programs this summer and will be taking his MCAT prior to medical school applications.

3. Niveditha Pinnamaneni: Radiology Findings in Patients Diagnosed with Breast Cancer Local Recurrence after Breast Conservation Treatment

Mentor: Lawrence Solin, MD

Nivi reviewed the mammogram films and reports from original cancer diagnoses and compared them to the findings at the time of local recurrence in order to analyze patterns of the appearance of both primary and recurrent tumors. Nivi completed her film and chart review of about 100 patients in collaboration with a breast radiologist, Susan Orel, MD. This project involved mainly descriptive statistics which Nivi performed herself. She compared the appearance of primary tumors to the recurrent tumors. She showed for example that primary tumors that were not visible on mammogram were in fact still likely to be visible on mammogram at the time of recurrence, showing that mammography is still useful for follow-up in this group of patients. The manuscript for this study is currently being written for peer-review publication.

4. Elizabeth Gurney: The Response of Human Cancer Cells to Sustained Anti-mitotic Therapy: The Uniqueness of Breast Cancer

Mentor: Gary Kao, MD PhD

Elizabeth continued to work with Dr. Kao after her summer session throughout her senior year. While her laboratory work remains in the preliminary stages, she was very inspired by her experiences investigating anti-mitotic therapy effects on breast cancer cells. Elizabeth will be attending New York University Medical School this fall.

5. Arber Kodra: Effect of Green Tea and Curcumin on Breast Cancer Cell Lines

Mentor: Gary Kao, MD PhD

Arber examined the radiosensitizing and anticancer properties of green tea and curcumin and found a complex response cascade in cell lines. For example, the anticancer properties of green tea may be related to transcription repression. Arber's work was submitted for presentation at the 2006 ASTRO meeting. Arber will also be attending Columbia Medical School this fall.

Update on Projects from 2004 and 2003:

Undergraduate researchers, 2004:

1. Jessica Liao: "Late Cardiac Effects of Breast Irradiation: An Analysis of Electrocardiograms"

Mentors: Eleanor Harris, MD and Candace Correa (medical student)

Status: Jessica completed data collection and preliminary analysis. She is co-author on several manuscripts currently under revision, including one specifically analyzing the EKG findings that Jessica collated. The overview analysis of this dataset has been accepted for publication by the Journal of Clinical Oncology, and two additional manuscripts are under review. Two additional manuscripts are in progress.

Jessica Liao initially completed this clinical research project in the summer training program; during the course of the program she was exposed to laboratory research, which kindled such interest that she performed Independent Study of mechanisms in cancer cells with Dr. Kao as part of her academic course load. A manuscript of her laboratory work is in revision. Jessica is currently a second year student at the University of Florida School of Medicine.

2. Chandresh Ladva: "The Survival of Patients with Past Histories of Malignancies Prior to Early Stage Breast Cancer"

Mentor: Eleanor Harris, MD

Status: Chandresh completed all data collection and statistical analysis. His project has been accepted for poster presentation at the Era of Hope Conference in Philadelphia in June 2005. Chandresh wrote a draft manuscript, and the data is currently being updated with a revised manuscript in progress. Chandresh continues his undergraduate studies at the University of Pennsylvania.

3. Rahn Voong: "Death and Degradation: Discovering the Molecular Determinants of Taxol Sensitivity"

Mentor: Gary Kao, MD, PhD

Status: Rahn is co-author on the following manuscript: Dowling M, Voong RK, Keutmann MK, Harris EE, Kao GD, "Mitotic Spindle Checkpoint Inactivation by Trichostatin A Defines a Mechanism for Increasing Cancer Cell Killing by Microtubule-Disrupting Agents". Cancer Biology & Therapy, Vol. 4 (2), In press, May 2005.

Rahn's research contributions were considerable and enabled not only her co-authorship on this project but also several others that have been submitted or are nearing completion including one in which she will be first-author. Rahn's experiences kindled such a strong desire to pursue cancer research, that she has devoted a year following graduation to continue her work investigating mechanisms relating to breast and other forms of cancer.

4. Kristin Meliambro: "An Analysis of Outcomes of Distant Metastases in Unusual Histologies of Breast Cancer"

Mentor: Lawrence Solin, MD

Status: Kristin completed the majority of data collection and preliminary analysis. Her work contributed also to the 2005 summer project completed by Daniel Feldman. The statistical analysis has been completed and the manuscript will be submitted for publication this year.

5. Andrea Denunzio: "Investigation of Cosmesis and Complications in Patients with DCIS"

Mentors: Lawrence Solin, MD and Neha Vapiwala, MD (resident)

Status: Andrea completed data collection and analysis. She will be co-author on a manuscript being written by a resident, Neha Vapiwala, with anticipated submission this year for peer-review publication.

6. Anil Maggee: "Density Determines Rapid Killing of Breast Cancer Cells by Taxol"

Mentor: Gary Kao, MD, PhD

Anil Maggee, the first student from outside Penn, solidified his desire to pursue a career as a physician. However, Anil was not able to complete a sufficient body of work for publication.

Update on Undergraduate Projects from 2003:

1. Jill Starzyk: "Analysis of biopsies performed after definitive irradiation for early stage breast cancer".

Mentor: Lawrence Solin, MD

Status: Accepted for poster presentation at the American Society for Clinical Oncology (ASCO) meeting in June 2004. Data is being updated and the manuscript is in preparation by a current resident.

Jill is currently a third year medical student at Northwestern University.

2. Eric A. Lee: "Outcomes after breast conservation therapy relative to Her2 expression" and "Factors that determine breast cancer cell resistance to the microtubule-disrupting drugs".

Mentors: Eleanor Harris, MD and Gary Kao, MD, PhD

Status: Clinical project accepted for oral presentation at the American Society for Therapeutic Radiology and Oncology (ASTRO) meeting in October 2004; "The Impact of Her2/neu Status on Local Recurrence in Women With Stage I-II Breast Cancer Treated With Breast Conservation Therapy", presented by Eleanor Harris, MD. The manuscript is in press at The Breast Journal.

First author on published manuscript: Lee EA, Keutmann MK, Dowling M, Harris EE, Chan G, Kao GD. "Mitotic Checkpoint Targets Human Cancer Cells to Killing by Microtubule- disrupting Drugs". *Molecular Cancer Therapeutics*,. Vol. 3(6): 661-669, 2004.

Eric is currently a third year medical student at Duke University.

3. Michael Keutmann: "Inactivation of the Mitotic Checkpoint Targets Human Cancer Cells to Killing by Microtubule-disrupting Drugs"

Mentor: Gary Kao, MD, PhD

Status: Co-author on published manuscript: Lee EA, Keutmann MK, Dowling M, Harris EE, Chan G, Kao GD. "Mitotic Checkpoint Targets Human Cancer Cells to Killing by Microtubule- disrupting Drugs". *Molecular Cancer Therapeutics*,. Vol. 3(6): 661-669, 2004.

Co-author on published manuscript: Dowling M, Voong RK, Keutmann MK, Harris EE, Kao GD, "Mitotic Spindle Checkpoint Inactivation by Trichostatin A Defines a Mechanism for Increasing Cancer Cell Killing by Microtubule-Disrupting Agents". *Cancer Biology & Therapy*, Vol. 4 (2), In press, May 2005.

Michael is attending graduate school.

4. Jordan Booty: "Time course of lymphedema development in breast cancer patients".

Mentors: Eleanor Harris, MD and Andrea Cheville, MD

Status: After Jordan completed his phase of the project, we decided to add some additional data points to the analysis. Data collection was continued in 2004 by a medical student, Neha Amin, who was supported by a grant from the NIH-funded Short Term Training Grants. She presented the updated work at the University of Pennsylvania School of Medicine Short Term Summer Research Student Symposium in August 2004. The project was updated by a clinical fellow, Voika Bar-Ad, and statistical analysis is completed. An analysis of patients with minimal lymphedema has been accepted for presentation at the 2006 annual meeting of the American Society for Clinical Oncology (ASCO). An analysis of the overall patterns of lymphedema time course has been submitted to the 2006 ASTRO meeting. Two manuscripts are under revision.

IV. Reportable Outcomes:

A. Meeting Presentations:

(Grant participants in bold):

Harris EE, Starzyk J, Solin LJ. “Results of biopsies performed after breast conservation therapy for stage I-II breast cancer”, *Proceedings ASCO*, Vol. 23: 86, 2004.

Ladva C, Harris EE, Hwang W-T, Solin LJ, “The Survival of Patients with Past Histories of Malignancies Prior to Early Stage Breast Cancer”. Accepted for poster presentation at the Era of Hope Conference, June 2005, Philadelphia, PA

Harris, EE. “Undergraduate Summer Training Program Investigating the Role of Radiation Therapy in Breast Cancer Clinical and Translational Research”, Accepted for poster presentation at the Era of Hope Conference, June 2005, Philadelphia, PA.

Bar Ad V, Cheville A, Amin N, **Booty J, Solin LJ, Harris EE.** “Minimal arm lymphedema after breast conservation therapy”, Accepted to ASCO, June 2006, Atlanta, GA.

Bar Ad V, Schultz D, Amin N, **Booty J, Solin LJ, Harris EE.** Arm lymphedema after breast conservation therapy, Submitted to ASTRO, October 2006, Philadelphia, PA.

Harris EE, Kasi S, Zhang Y, Solin LJ. “The Role of Anemia in Local Control After Breast Conservation Therapy for Early Stage Breast Cancer”, Submitted to ASTRO, October 2006, Philadelphia, PA.

Kao GD, Kodra A, Kim M, Solin LJ. “Effects of Green Tea Extract on Protein and mRNA expression in Human Breast Cancer Cells: Impairment of the DNA damage response?” Submitted to ASTRO, October 2006, Philadelphia, PA.

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B. Publications - Published or In Press:

Lee EA, Keutmann MK, Dowling M, Harris EE, Chan G, Kao GD. “Mitotic Checkpoint Targets Human Cancer Cells to Killing by Microtubule-disrupting Drugs”. *Molecular Cancer Therapeutics*,. Vol. 3(6): 661-669, 2004.

Dowling M, **Voong RK, Keutmann MK, Harris EE, Kao GD,** "Mitotic Spindle Checkpoint Inactivation by Trichostatin A Defines a Mechanism for Increasing Cancer Cell Killing by Microtubule-Disrupting Agents". *Cancer Biology & Therapy*, Vol. 4 (2), 197-206, 2005.

Harris EE, Hwang W-T, Lee EA, Cengel K, DeMichele A, Solin, LJ. “The Impact of Her2/neu Status on Local Recurrence in Women With Stage I-II Breast Cancer Treated With Breast Conservation Therapy”, *The Breast Journal*, In press, May 2006.

Harris EE, Correa C, Hwang W-T, Liao J, Litt HI, Ferrari VA, Solin LJ. “Late Cardiac Mortality and Morbidity in Early Stage Breast Cancer Patients after Breast Conservation Treatment”. In press, *Journal of Clinical Oncology*, May 2006

C. Manuscripts in Progress:

Orel S, **Pinnamaneni N, Harris EE, Solin LJ.** “Radiology Findings in Patients Diagnosed with Breast Cancer Local Recurrence after Breast Conservation Treatment”.

Harris EE, Feldman D, Meliambro K, Schultz D, Solin LJ. “Patterns of Metastatic Disease in Unusual Breast Cancer Histologies Treated for Early Stage Breast Cancer”.

Vapiwala N, **Denunzio A, Feldman D, Harris EE, Solin LJ.** “Cosmesis and Complications in Patients with DCIS Treated with Breast Conservation Therapy”

Vapiwala N, Hwang W-T, **Harris EE, Starzyk J, Solin LJ.** “Results of biopsies performed after breast conservation therapy for stage I-II breast cancer”.

Harris EE, Ladva C, Hwang W-T, Solin LJ. “The Survival of Patients with Past Histories of Malignancies Prior to Early Stage Breast Cancer”.

Bar Ad V, Cheville A, Amin N, **Booty J, Solin LJ, Harris EE.** “Minimal arm lymphedema after breast conservation therapy”.

Bar Ad V, Schultz D, Amin N, **Booty J, Solin LJ, Harris EE.** Arm lymphedema after breast conservation therapy”.

V. Conclusions:

In this third and final year of the undergraduate training grant, I had the largest applicant pool, and a highly motivated and productive group of student researchers. As this annual report details, many of their projects will be presented at research meetings and published in peer-reviewed medical journals. In addition, many of the participants are in medical school or preparing to apply. The students universally attribute their research experience with increasing their interest in medical and research careers.

The three year breast cancer oriented summer training grant has been a huge success in meeting the goals of providing undergraduate students interested in medical or research careers a comprehensive research experience and in igniting their passion for a future career in medicine and research. Several students have stayed on to do additional clinical or bench research after their summer project was completed. Hopefully many will remember their experiences working with breast cancer patients and studying their outcomes and be inspired to pursue careers in breast cancer treatment and research.

The biggest challenge for me as principal investigator has actually been getting the immense research output of these students into publication. Ultimately I expect that most of the projects the students completed will be published. It has simply taken me time to write the manuscripts, an effort I will continue to complete after the grant period. To this end I have enlisted the help of another junior faculty person to assist in writing up some of the projects so that the students efforts will all result in published manuscripts.

It was with great disappointment that I learned this grant mechanism was to be discontinued because I believe it has been a highly productive training grant. I hope that it may be offered again in the near future.

VI. References:

A. Publications - Published or In Press:

(Grant participants in bold):

Lee EA, Keutmann MK, Dowling M, **Harris EE**, Chan G, **Kao GD**. “Mitotic Checkpoint Targets Human Cancer Cells to Killing by Microtubule-disrupting Drugs”. *Molecular Cancer Therapeutics*,. Vol. 3(6): 661-669, 2004.

Dowling M, **Voong RK, Keutmann MK, Harris EE, Kao GD**, "Mitotic Spindle Checkpoint Inactivation by Trichostatin A Defines a Mechanism for Increasing Cancer Cell Killing by Microtubule-Disrupting Agents". *Cancer Biology & Therapy*, Vol. 4 (2), 197-206, 2005.

Harris EE, Hwang W-T, **Lee EA**, Cengel K, DeMichele A, **Solin LJ**. “The Impact of Her2/neu Status on Local Recurrence in Women With Stage I-II Breast Cancer Treated With Breast Conservation Therapy”, *The Breast Journal*, In press, May 2006.

Harris EE, Correa C, Hwang W-T, **Liao J**, Litt HI, Ferrari VA, **Solin LJ**. “Late Cardiac Mortality and Morbidity in Early Stage Breast Cancer Patients after Breast Conservation Treatment”. In press, *Journal of Clinical Oncology*, May 2006

B. Meeting Presentations:

Harris EE, Starzyk J, Solin LJ. “Results of biopsies performed after breast conservation therapy for stage I-II breast cancer”, *Proceedings ASCO*, Vol. 23: 86, 2004.

Ladva C, Harris EE, Hwang W-T, Solin LJ, “The Survival of Patients with Past Histories of Malignancies Prior to Early Stage Breast Cancer”. Accepted for poster presentation at the Era of Hope Conference, June 2005, Philadelphia, PA

Harris, EE. “Undergraduate Summer Training Program Investigating the Role of Radiation Therapy in Breast Cancer Clinical and Translational Research”, Accepted for poster presentation at the Era of Hope Conference, June 2005, Philadelphia, PA.

Bar Ad V, Cheville A, Amin N, **Booty J, Solin LJ, Harris EE**. “Minimal arm lymphedema after breast conservation therapy”, Accepted to ASCO, June 2006, Atlanta, GA.

Bar Ad V, Schultz D, Amin N, **Booty J, Solin LJ, Harris EE**. Arm lymphedema after breast conservation therapy, Submitted to ASTRO, October 2006, Philadelphia, PA.

Harris EE, Kasi S, Zhang Y, Solin LJ. “The Role of Anemia in Local Control After Breast Conservation Therapy for Early Stage Breast Cancer”, Submitted to ASTRO, October 2006, Philadelphia, PA.

Kao GD, Kodra A, Kim M, Solin LJ. “Effects of Green Tea Extract on Protein and mRNA expression in Human Breast Cancer Cells: Impairment of the DNA damage response?” Submitted to ASTRO, October 2006, Philadelphia, PA.

Appendix: 2005 Flyer**Undergraduate Breast Cancer Research Opportunity**

Release: January 2005

The Department of Radiation Oncology at the University Of Pennsylvania School Of Medicine is pleased to announce a research opportunity for undergraduates at the University of Pennsylvania to participate in investigative projects in the area of breast cancer research. The training program will provide a broad range of opportunities for students to participate in general clinical or basic science breast cancer research. The student will be exposed to the research process from design to analysis to authorship, with the goal of instilling both an understanding of the research process and of fostering a lasting commitment to the pursuit of breast cancer research.

Due to a generous grant from the Department of Defense Breast Cancer Research Program, we are able to offer a \$4000 stipend to up to six undergraduates students able to spend 12 weeks participating in a full-time mentored research project. (For interested students, additional independent study during the academic year may be available.) The program director is Eleanor Harris, MD, assistant professor of Radiation Oncology. In order to apply for the training program, students must be in good academic standing at the university. Students are required to fill out an application form and to submit an unofficial transcript. Students must also submit a one-page essay describing their reasons for applying to the training program, in particular their motivation for conducting breast cancer research. Applications will be due no later than March 18, 2005.

Students requesting laboratory projects involving bench research will be required to have some prior experience in basic laboratory techniques involved in their experiments, as 12 weeks is too brief to allow training in techniques and the completion of a set of experiments. For students interested in clinical projects, no prior research experience will be required. In fact, it is anticipated that the training program will provide many of these students with their first exposure to high quality scientific research with expert faculty mentoring

Dr. Harris will review the applications and choose participants based on their interests, commitment, academic record, motivation and future goals. Applicants will be informed of their acceptance by April 2005. Shortly afterwards, each participant will meet with Dr. Harris to discuss their background, areas of interest and potential research ideas. If the student has a specific research project or faculty member in mind, he or she will be put in contact with the appropriate mentor. While the primary mentor must be a training program faculty, students may be assigned a co-mentor from another department if beneficial. If the student does not have a specific research goal at the initial meeting, he or she will be given a list of projects with brief descriptions to review and will be asked to choose three projects from that list. Dr. Harris will review all the requests and assign a project to each participant. The student will then meet with that faculty mentor to discuss the specific project. The student will be assigned background reading, and with the mentor's guidance will be asked to develop a timeline for research plan. It is anticipated that participants will complete these steps during the spring semester and prior to beginning their project in the summer session.

To request an application, please contact Ms. Betsy Patton in the Department of Radiation Oncology by phoning 215-662-3094, or by writing to email address: patton@xrt.upenn.edu.

Appendix: Project List

Undergraduate Breast Cancer Research Training Grant Project List

This page lists the available projects for undergraduates participating in the training program by title and faculty mentor. Individual projects are suitable for the student to conduct alone under the mentor's guidance. Collaborative projects would be carried out with a medical student or resident. All laboratory projects are anticipated to be collaborative. Students may also propose original research ideas to the program director.

A. Clinical Radiation Oncology Research Projects, Individual

1. Sequencing of taxanes with radiation therapy.
2. Efficacy of Biafene in reducing moist desquamation in large breasted women undergoing radiation therapy.
3. Changes in blood counts during breast or chest wall irradiation.
4. Outcomes after breast conservation therapy depending on method of cancer detection.
5. Findings in post-treatment biopsies after breast conservation treatment.
6. Outcomes for patients with isolated brain metastases versus multiple sites of metastatic disease.
7. The time course of lymphedema development in breast conservation patients.

B. Clinical Radiation Oncology Research Projects, Collaborative

1. The long term incidence of late cardiac and pulmonary sequelae after breast conservation therapy
2. The relationship of socioeconomic status to outcomes in women treated with radiation for breast cancer.
3. Measures of clinical and subclinical lymphedema compared to upper extremity MRI.
4. The relationship of wedge angle and position to contralateral breast cancer after unilateral whole breast irradiation.
5. The impact of breathing motion on heart and lung volumes in while breast irradiation.
6. Outcomes of breast conservation therapy in ductal carcinoma in situ.
7. Incidence of contralateral breast cancer relative to age of breast cancer diagnosis.
8. Postoperative complications after salvage mastectomy for local recurrence.
9. Hemoglobin levels at time of presentation for breast cancer therapy and impact of locoregional radiation.

C. Basic Science Research Projects

1. The impact of Her2 and Her1 overexpression in outcomes after breast conservation therapy. (Harris)
2. Relationship of Akt and Her1 protein expression to the risk of local recurrence after breast conservation therapy. (Gupta)
3. Regulation of vascular endothelial growth factor (VEGF) in breast cancer. (Maity)
4. Control of hypoxia-inducible Factor-1 (HIF-1) expression in breast cancer. (Maity)
5. Chromatin modifications determine chemotherapy and radiation sensitivity in human breast cancer cells. (Kao)
6. Critical components of the DNA damage response in breast cancer cells: novel proteins recruited to sites of damage. (Kao)

D. Physics Projects

1. Dose volume histogram (DVH) analysis of breast volume retrospectively contoured on CT, treated with conventionally placed treatment fields.
2. Selection of energy, wedge angle and bolus in radiotherapy as a function of breast size.
3. IMRT (Intensity Modulated Radiation Therapy) treatment planning and delivery techniques for treatment of the breast and regional nodes.
4. Comparison of techniques for partial breast irradiation.

Appendix: Orientation Agenda and Lecture Series

**Orientation
Breast Cancer Summer Research Program**

May 23, 2005

2 Donner Conference Room

09:00 - 09:30	Betsy Patton, Program Coordinator Welcome and Introduction
09:30 - 10:00	Mark Patrick, Research Division Employment Forms
10:00 - 11:00	Peggy Alfarano HIPPA Orientation
11:00 - 12:00	Questions for Betsy Patton regarding Program
12:00 – 1:00	Lunch in Founders A
01:00 – 01:30	Obtain Photo Ids
01:30 - 05:00	Eleanor Harris, MD Basic Principles of Radiation Oncology

May 24, 2005

2 Donner Conference Room

09:00 – 09:30	Betsy Patton, Program Coordinator
09:30 – 10:00	Linda Miller, BSN, RN Director of Nursing Clinical Research Clinical Research Practices
10:30 – 11:30	Ralph Ferro IT Manager Orientation to Information Systems
11:30 – 12:00	Keith Cengel, MD Resident Lecture- Effects of Her2 Overexpression in Breast Conservation Therapy
12:00 – 01:00	Lunch in Donner Conference Room

- 01:00 – 02:00 Rebecca Davidson, MD
Lecture- Adjuvant Therapy for Breast Cancer
- 02:00 – 03:00 Chandresh Ladva
Lecture- The Survival of Patients with Past Histories of
Malignancies Prior to Early Stage Breast Cancer

May 25, 2005

2 Donner Conference Room

- 08:30 – 09:00 Betsy Patton, Program Coordinator
- 09:00 - 09:30 Vasthi Christensen, MD Resident
Lecture- Impact of concurrent versus sequential Tamoxifen
- 10:00 – 11:30 E. Paul Wileyto, PhD
Lecture- Introduction to BioStatistics
- 11:00 – 12:00 Betsy Patton, Program Coordinator
Review Data Coding
- 12:00 – 01:00 Lunch in Founders B
- 01:00 – 02:45 Show students to work stations
- 03:00 – 05:00 Gary Kao, MD, PhD
Scientific Research Methods
(John Morgan Bldg- 195 Conference Room)

Appendix: Student Research Symposium Announcement

**Undergraduate Breast Cancer Summer Research Program
Symposium**

To: Radiation Oncology
From: Eleanor Harris, MD
When: Friday, August 12, 2005
Where: 2 Donner Conference Room
Time: 1st session from 8:00 – 9:00am
2nd session from 12:00 – 1:00pm

A continental breakfast will be provided for the morning session and lunch will be provided at noon.

The topics will be:

1st session

- **The Response of Human Cancer Cells to Sustained Anti-mitotic Therapy: The Uniqueness of Breast Cancer**

Elizabeth Gurney

Mentor: Gary Kao, MD, PhD

- **Effect of Green Tea and Curcumin on Breast Cancer Cell Lines**

Arber Kodra

Mentor: Gary Kao, MD, PhD

2nd session

■ **The Impact of Anemia on Local Control and Survival of Breast Cancer Patients Receiving Radiation Therapy**

Sundeep Kasi

Mentor: Eleanor Harris, MD

■ **Radiology Findings in Patients Diagnosed with Local Recurrence Breast Cancer**

Niveditha Pinnamaneni

Mentor: Lawrence Solin, MD

■ **Analysis of Metastatic Disease by Histological Subtype in Early-Stage Breast Cancer Patients**

Daniel Feldman

Mentor: Eleanor Harris, MD

Appendix: Student Evaluation FormBreast Cancer Research in Radiation Oncology – 2005 Summer Training Program
Evaluation Form

Name: _____ Date: _____

Faculty Mentor: _____

Project Title: _____

Part A: For the following aspects of the summer research training program, please choose the best option describing the quality of each part of the program, if applicable to your project:

	Excellent	Good	Satisfactory	Inadequate
1. Breast cancer introductory lecture series				
2. Departmental/Hospital orientation				
3. Research methods and design				
4. Clarity of research project				
5. Mentoring and oversight				
6. Access to mentor				
7. Scope of research project appropriate				
8. Shadowing a clinician				
9. Support staff/ file room access				
10. Laboratory facilities				
11. Supplies				
12. Office/computer facilities				
13. Interaction with residents/students				
14. Technical services				
15. Interaction with department personnel				

Part B: Please assess the following goals of the research training program, and whether they were accomplished during the program:

1. Did the program provide an opportunity to learn more about breast cancer research?
2. Was the project you were assigned or designed of the appropriate scope and level of difficulty?

3. Was the project of sufficient interest to you?
4. Did the program increase your interest in medical research?
5. Did the program increase your interest in breast cancer research?
6. Did the program change or affect your educational or intellectual goals? If so, how?
7. What do you think were the goals of your research program, and were they met?
8. Would you recommend this program to a peer?

Part C: Your comments and suggestions will be very helpful in improving the quality of the research training program. Please discuss any of your ideas for improvements or suggestions for changes.

Appendix: Submitted Abstracts in 2005 for Student Research Projects

The Role of Anemia in Local Control After Breast Conservation Therapy for Early Stage Breast Cancer

Eleanor E. R. Harris, **Sundeep Kasi**, Yawei Zhang, Lawrence J. Solin

Purpose: Anemia has been associated with poorer local control and survival in patients treated with both surgery and radiation for cervical and head and neck cancers. This study was undertaken to assess the impact of anemia at the time of radiation treatment on local recurrence and other outcomes in women who have undergone breast conservation therapy for early stage breast cancer.

Methods: Medical records were reviewed for all consecutive patients with stage 0, I and II breast cancer treated with lumpectomy and irradiation between 1977 and 2002. Patients were excluded if they had a prior contralateral breast cancer or other prior malignancy, and if they had no recorded hemoglobin levels, lacked a baseline or had only one hemoglobin value, or received less than 6000 cGy total radiation dose. Of this cohort of 1368 patients, 10% were stage 0 (ductal carcinoma in situ or DCIS, N=139), and 90% were stage I or II invasive carcinomas (N=1229). Hemoglobin levels were recorded at baseline (within 1 month prior to the start of radiation) and during radiation (at week 3 to 4). Anemia was defined as a hemoglobin level less than 12 gm/dL. Using this cut-off value for the baseline hemoglobin, the cohort was divided into two groups: normal and anemic. Median age was 54 years in both groups. Median follow-up was 6.5 years.

Results: Of the 1368 eligible patients, 240 (17%) were anemic and 1128 (83%) had a normal baseline hemoglobin. The majority of anemic patients had mild anemia, with hemoglobin levels between 10 and 11.9 gm/dL; only 22 (1.6%) patients had a baseline hemoglobin <10 gm/dL. Anemia was recorded in 290 (21%) of patients during radiation. When patient characteristics were compared, the anemic group was significantly more likely to have size T2 tumors, positive nodes, ER and PR negative tumors, to have received nodal radiation, and to have received chemotherapy (all $p \leq 0.01$). When the comparisons were controlled for the use of chemotherapy prior to radiation, there was no longer a significant difference in T stage, ER or PR status. Among patients who received chemotherapy prior to radiation, 44% were anemic, a significantly higher rate than for those who had post-radiation chemotherapy (16%) or no chemotherapy (14%; $p < 0.0001$). There was no statistically significant difference in unadjusted rates of local-regional recurrence, overall survival, cause-specific survival, relapse free survival, or distant metastases between the anemic and normal groups (all $p \geq 0.15$; see Table).

Conclusions: Patients with early stage disease presenting for radiation are more likely to be anemic if they have received prior chemotherapy, but the majority will have mild anemia with hemoglobin levels between 10 and 11.9 gm/dL. Mild anemia during radiation had no significantly adverse impact on local recurrence or survival in early stage breast cancer patients undergoing breast conservation therapy.

Table 1: Outcomes by Hemoglobin Level at Pre-radiation Baseline

Outcome	Anemic	Normal	P-value
Local recurrence			
5 Years	3%	3%	0.24
10 Years	9%	9%	
15 Years	19%	12%	
Overall survival			
5 Years	88%	90%	0.29
10 Years	72%	79%	
15 Years	60%	66%	
Cause specific survival			
5 Years	91%	94%	0.17
10 Years	85%	88%	
15 Years	77%	84%	
Relapse free survival			
5 Years	85%	86%	0.15
10 Years	74%	79%	
15 Years	61%	71%	

Arm lymphedema after breast conservation treatment

V. Bar Ad, D. Schultz, N. Amin, **J. Booty**, L.J. Solin, E.E. Harris

Department of Radiation Oncology, Hospital of the University of Pennsylvania, Philadelphia, PA

Background: Arm lymphedema (ALE) is a potential side effect of the treatment for breast carcinoma. Although the rate of lymphedema is decreasing with the use of sentinel node biopsy, patients with prior treatment or those who currently require axillary dissections remain at risk for lymphedema. The objective of the current study was to analyze the time-course of ALE and the influence of the potential risk factors on the time-course of ALE after breast conservation treatment for the breast cancer.

Methods: The study cohort was drawn from stage I or II patients who, between 1977 and 2002, underwent breast conservation therapy including axillary lymph node dissection or sentinel lymph node biopsy, in the later years of the study, followed by radiation.

ALE was documented in 266 of 1713 (15%) patients. All 266 patients received breast irradiation. Breast and regional nodal irradiation was delivered in 32 % (85/266) of cases. During follow up assessments after treatment, measurements of arm circumference were performed at regular intervals, for clinically evident swelling of the arm or for complaints of swelling of the arm.

Results: The median age of patients was 54 years. The median interval to develop ALE was 1 year (range 0.1-7.5 years). The median follow up was 11 years.

ALE was scored at presentation as minimal, mild, moderate/severe in 39% (105/266), 49% (129/266), and 12% (32/266) of the patients, respectively.

21% (22/105) of the patients with minimal ALE progressed to more severe grades of ALE after 1 year of follow-up, despite the treatment for ALE in 41% of them. 50% (65/129) of the patients with mild ALE had no improvement or progressed at 1 year follow up, despite the treatment for ALE in 32% of them. 56% (18/32) of the patients with moderate/severe ALE at presentation had no improvement or progressed at 1 year follow up, despite the treatment for ALE in 71% of them.

Of the patients more than 70 years old at the time of breast cancer diagnosis, 20% (6/30) had moderate/severe ALE at presentation, in comparison with only 12% (4/33) of the patients who were less than 39 years old. 30% (9/30) of the patients more than 70 years old had moderate/severe ALE at 1 year of follow up, in comparison with only 6% (2/33) of the patients who were less than 39 years old.

17% (12/72) of the patients with a BMI > 30 kg/m² at diagnosis developed moderate/severe ALE in comparison with only 6% (6/89) of the patients with a BMI < 25 kg/m². 22% (16/72) of the patients with a BMI > 30 kg/m² had moderate/severe ALE at 1 year of follow up, in comparison with only 11% (10/89) of the patients with a BMI < 25 kg/m².

Conclusions: This cohort documents the potential for patients with ALE to progress to more severe grade of ALE and the influence of age and BMI to the time-course of ALE.

Table. Pattern of progression after 1 year of follow up (w/ or w/o treatment)

Grade at presentation	Minimal at 1 year	Mild at 1 year	Moderate/Severe at 1 year	No measurements at 1 year
Minimal < 2 cm	66%	12%	9%	13%
Mild 2-2.99 cm	40%	40%	10%	10%
Moderate/Severe > 3cm	24%	9%	56%	9%

Minimal arm lymphedema after breast conservation therapy

V. Bar Ad, A. Cheville, N. Amin, **J. Booty**, L.J. Solin, E. Harris

Departments of Radiation Oncology and Physical Medicine and Rehabilitation, Hospital of the University of Pennsylvania, Philadelphia, PA

Background: Arm lymphedema (ALE) is a serious consequence of the treatment for breast carcinoma. The objective of the current retrospective study was to analyze the time-course of minimal ALE after breast conservation treatment for early stage breast cancer.

Methods: The study cohort was drawn from consecutive stage I or II patients who underwent breast conservation therapy including axillary staging followed by radiation. During follow-up assessments after treatment, measurements of arm circumference were frequently performed at regular intervals, for clinically evident swelling of the arm or for complaints of swelling of the arm. ALE was documented in 274 of 1861 (14%) patients. 109 patients, 6% of overall group, and 40% of the patients with lymphedema, presented with minimal ALE, defined as a difference of 2 cm or less between the affected and unaffected arms.

Results: The median age of patients was 54 years. The median interval to develop ALE was 1 year. The median follow up was 11 years. Among all 109 patients with minimal grade ALE at the time of ALE diagnosis, 21%, 13% and 14% of the patients progressed to more severe grades of lymphedema after 1,3 and 5 years of follow-up, respectively (See table). 40% of the patients with minimal grade ALE received therapy for lymphedema. Despite treatment for minimal grade ALE, 37% of treated patients progressed to more severe grades of lymphedema at 1 year follow up, and 24% progressed at 3 and 5 years follow up.

Conclusions: Minimal ALE after breast conservation therapy, including axillary staging, developed in 6% of stage I or II breast cancer patients. Minimal ALE has the potential to progress to more severe grade of ALE. Despite treatment for lymphedema for minimal grade ALE, some patients still progressed to more severe grades of lymphedema.

Table. Pattern of progression of patients with minimal grade ALE at presentation

Time after presentation	Minimal < 2 cm	Mild 2-2.99 cm	Moderate/Severe > 3cm	No measurements
1 year	65%	12%	9%	14%
3 years	45%	5%	8%	42%
5 years	34%	7%	7%	52%

Effects of Green Tea Extract on Protein and mRNA expression in Human Breast Cancer Cells: Impairment of the DNA damage response?

G. D. Kao*¹, **A. Kodra***², M. Kim*¹, L. J. Solin*¹, ¹*Hospital of the University of Pennsylvania, Philadelphia, PA*, ²*University of Pennsylvania, Philadelphia, PA*,

Introduction

The use of complementary/alternative therapies such as green tea by patients undergoing treatment for cancer has been extensively documented. However, little is known about how such practices influence the response to radiation, an integral component of the treatment for many malignancies, including breast cancer. We therefore investigated the effects of green tea extract (GTE) on human breast cancer cells.

Methods

MCF7 and SKBR3 cells were exposed to GTE at varying concentrations and for different lengths of time. Mock- and GTE-exposed cells were assessed for cellular growth. Cell cycle and viability status were assessed via flow-assisted cytometric analysis (FACS), complemented with propidium iodide exclusion and clonogenic survival assays. Levels of the transcription factor Sp1, and the DNA-damage-related proteins ATM, Rad51, Mre11, and BRCA1 were determined via Western blotting. mRNA levels were assessed via reverse-transcriptase polymerase chain reaction. BRCA1 promoter activity was assessed via a luciferase-based reporter.

Results

GTE led to decreased cell growth and increased death of both cell lines in a dose-dependent manner. Interestingly, Sp1, ATM and BRCA1 protein levels were substantially diminished by GTE in both cell lines while Mre11 was largely unaffected, and Rad51 was diminished only in MCF-7. Both cell lines were radiosensitized by GTE. The decrease in BRCA1 protein was associated with decreased mRNA levels, as well as reduced BRCA1 promoter activity. **Conclusions** The anticancer effects of green tea may be due at least in part to transcription repression, through decreased Sp1 levels as well as reduced promoter activity. These mechanisms may contribute to decreased levels of DNA repair proteins, potentially leading to radiosensitization. If cancer-specific, these findings may provide reassurance that ingestion of green tea does not impair the anti-breast cancer efficacy of radiation therapy.